مجلة جامعة بابل / العلوم الصرفة والتطبيقية / العدد (2) / المجلد (17) : 2009

Synthesis of Some New N-(3-phthalidyl) Amines via Condensation Reaction of 3-Ethoxyphthalide with substituted Amino Pyridine.

Ala'a J. Mahrath
Clinical Biochemistry Department , Faculty of Medicine , Babylon University

Abstract

A series of substituted N-(3-phthalidyl) amines (NPA) were prepared via condensation reaction of 3-ethoxyphthalide (3-EP) with different substituted amino pyridine (2-amino, 3-amino, 3-hydroxy-2-amino, 4-methyl-2-amino, 5-nitro-2-amino, 5-chloro-2-amino and 5-bromo- 2-amino)pyridine.

The condensation reaction occurred selectively at (C-3) of the lactol form of the (3-EP) and no Schiff bases (SB) were detected. All the new compounds were characterized by spectroscopic and elemental analysis tools.

الخلاصة

تم تحضير سلسلة معوضاتN-(3-فثاليدايل)امين (NPA) من خلال تفاعل تكاثف 3- أيثوكسي فثاليد (3-EP) مع معوضـات البريدين امين المختلفة (2-امينو ، 3-امينو، 3-هيدروكسي -2-امينو ،4-مثيل- 2-امينو، 5-نترو- 2-امينو، 5-كلورو -2-امينو و5-بروموـ 2-امينو) بيريدين. حدثت التفاعلات بشكل انتقائي على ذرة الكربون في الموقع رقم 3 لحلقة اللاكتول العائدة للمركب (3-EP). وهذا يشير الى ان جميع نواتج المركبات المتكونه هي من نوع(NPA) وليس هنالك اي وجود لقواعد شـيف (SB).كما وان جميع المركبات المحضرة تم تشخيصها بواسطة طيف الاشعة تحت الحمراء وتحليل العناصر(C,H,N).

Introduction

Many derivatives of phthalide (A) have been reported because of these derivatives possess a very useful industrial and biological application. (Wheeler and Young,1961) reported diphenyl aminophthalide. (Kenneth and Koch, 1983) reported that the reaction of 3-halophthalides with cyclic secondary amines afforded N-(o-formylbenzoyl) amines. These compounds are useful as toxicants in fungicidal, germicidal and herbicidal compositions.

(Lin *et al.*,1982) reported that phthalide moiety is the principal ant asthmatic component of phthalide derivatives. He also reported that 3-aryphthalide shows a potent antagonistic effect on acetylcholine and histamine-induced trachea muscle constriction. Ogawa and Chim, 1988). prepared 4, 5-dimethoxyphthalide which was shown to be useful as a blood viscosity reducing agent.

The compound "3-phenylphthalide" has been used as a precursor in synthesis of some biologically active compounds that possess antihypertensive , vasorelaxant effect (Tis and Tan, 1997), and anti-inflammatory effect through protection of ischemic sites following ischemic brain injury (Xu and Feng, 2000) and anthracyclone systems(Giovanni& Giuseppe, 1990).

Furthermore n-butylphthalide (NBP) played a main role in production of vasoactive substances by cerebral and aortic endothelial cells (Zhongguo, 1999), inhibiting apoptosis and might have the potential to be a new anti apoptotic candidate for the treatment of ischemic cerebrovascular and neuron degenerative diseases(Qing & Xiao,2002), and as cerebral ischemic protective agent(Zhang *et al.*,1999).

It is known that "O-phthaladehydic acid (A) or o-formylbenzoic acid exists in equilibrium state with its lactone structure (B)(Watanbe,1976) which is known as: 3-hydroxyphthalide. (See scheme 1). (Bell & Cox, 1971).reported that in aqueous

solution o-formylbenzoic acid exists in about (93%) as 3-hydroxyphthalide. This result was based on the (**p**ka) studies.

Recently (Ra'ad Al-Hamdany *et al.,* 2003) reported new series of phthalidylamine and O-benzoylbenzamide derivatives which were proved to possess Genotoxic, antifungal and antibacterial activity. For these and other reasons, the synthesis of newly N-3-phthalylamine and its derivatives and the study of their properties got our interest.

Experimental

3-ethoxyphthalide was prepared according to previously published method[7].Melting point were measured by electro thermal melting points apparatus and were uncorrected Infrared spectra were recorded on Py-Unicom SP300 spectrometer as KBr discs.

All the solvents used were distilled and dried prior to use.

Results and discussion

It's noticed that infrared spectrum of the corresponding compound (B) revealed the presence of very strong absorption at (1730–1750) cm^{-1} due to lactonic carbonyl group. This source of tautamerism is illustrated in scheme (1).

Furthermore the presences of mineral acids (H_2SO_4, HCl) accelerate the formation of (B) form, as show in scheme (2).

Condensation reaction of compound (B) with ethanol in presence of con.H_2SO_4 as catalyst afforded the corresponding (3-EP) in high yield .IR spectrum shows the absence of the stretching frequency of hydroxyl group and presence of absorption at (1090- 1100)cm^{-1} due to ether group and strong absorption at (1765-1773) cm^{-1} due to lactonic group and . The reaction equation represented in scheme (3).

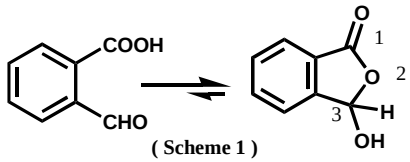
The reaction of (3-EP) with some primary amines (2-amino, 3-hydroxy-2-amino, 4-methyl-2-amino, 5-chloro-2-amino, 5-bromo-2-amino, 5-nitro-2-amino, and 3-amino) pyridine under refluxing conditions in presence of C_2H_5OH illustrated according to the general equation in scheme (4).

In most cases of the reaction studied crystals like needles were obtained. The physical and spectral data of the isolated phthalide amines are given in (Table1, 2 and 3).

Moreover the TLC of the crude product indicated that there is only single component developed which is means either (NPA) or (SB) was form. On the other hand the I.R spectrum of the isolated products (Table 2) shows the presence of two strong absorption bands in the range of (3320 – 3140)cm^{-1} due to (N-H) stretching of amine group and (1760 -1730)cm^{-1} ,due to (C= O) stretching of the lactonic group. These results indicate the formation of (NPA) only.

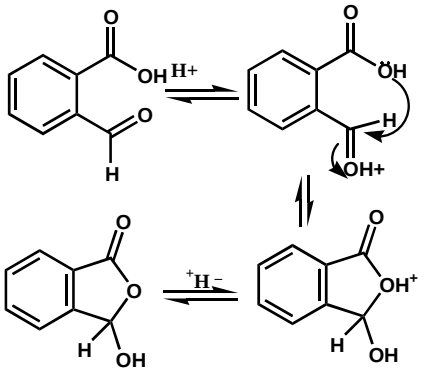
The only one exception in case of 3-hydroxy -2-aminopyridine which showed two peaks coupled in (3320 &3230) cm^{-1} due to (O-H & N- H) respectively. And low stretching frequency of the (C = O) group was in the range of(1715)cm^{-1} . For more information (see Table 2) this can be attributed to the possibility of the hydrogen bonding with the oxygen of the lactonic group. The elemental analysis of the proposed compounds gave us approximately the same suggested ratio table 3.

We can conclude these compounds can only formed if the additive (amines) react with lactol form of the comp. (EP) through SN^2 mechanism on position Carbon no.3.The reaction mechanism illustrated in (scheme 5).

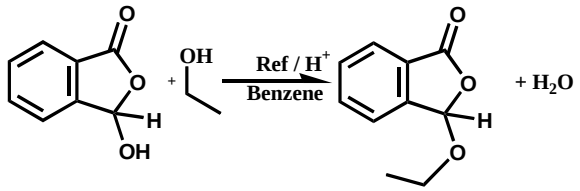


(Scheme 1)

(A) **(B)**

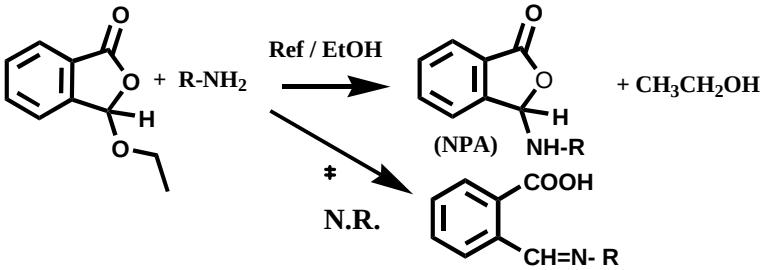


(Scheme 2)



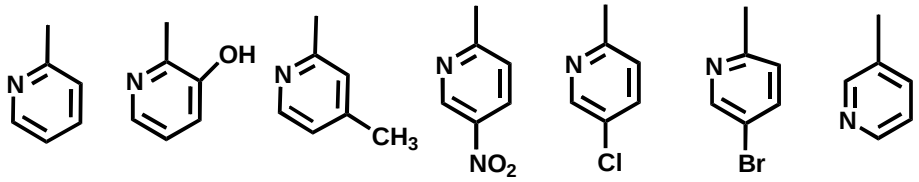
(EP)

(Scheme 3)



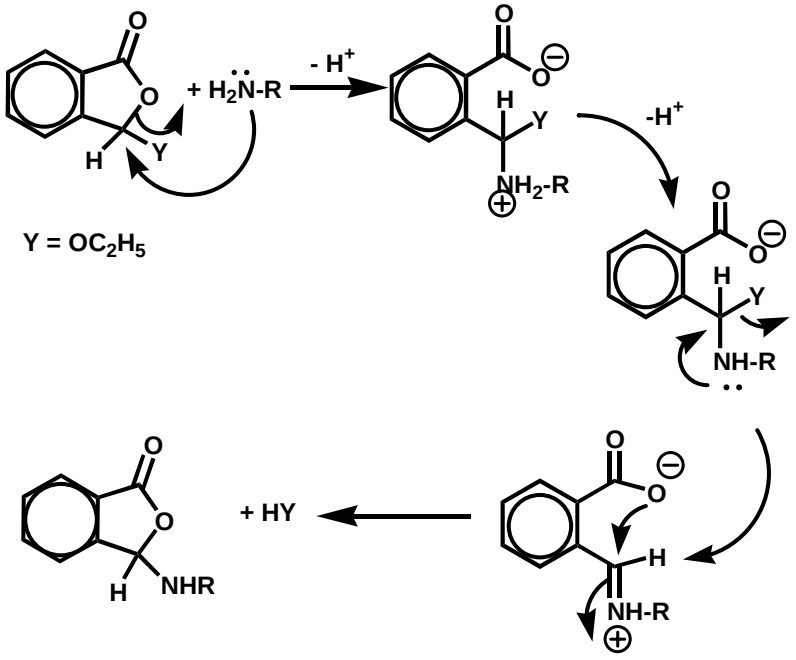
Schiff base

R = 1; , 2 , 3 , 4 , 5 , 6 , 7



(Scheme 4)

Reaction Mechanism



(Scheme 5)

Synthesis of 3-ethoxyphthalide (EP).

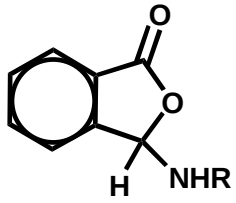
Procedure

A mixture of O-phthalaldehydic acid (5g, 660mmole), 25 ml absolute ethanol, 5-6 drops conc. H_2SO_4 and 35ml benzene were refluxed for 4 hr ..The mixture was cooled and 50ml of dry ether was added, then saturated $NaHCO_3$ solution (2× 10 ml) was added. The organic layer was separated dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent under vacuum afforded amorphous product (5.3g, 91%).Treatment the product with hot petroleum-ether (40-60) C°afforded a white needles(3.9g, 72%), m.p= 68C°. IR (KBr, cm^{-1})1765 (lactonic group).

Reaction of (EP) with substituted amino pyridines

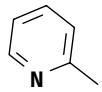
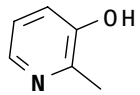
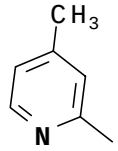
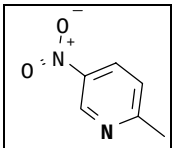
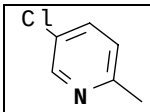
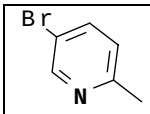
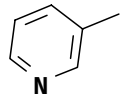
General procedure:

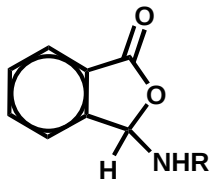
A mixture of (0.645g,5 mmole) EP and (5 mmole) amine in ethanol (12.5ml), was refluxed (3- 5) hr, then cooled in ice-bath. In certain cases a solid product starts to appear. Otherwise; evaporating the solvent or filtration afforded the product which was then recrystallized. Table 1.



(General Structure)

Table (1) Some physical data of (NPA).

No.	R Group	Molecular Formula	m.p(C)°	Yield %	Solvent cryst.	Molecular weight
1		$C_{13}H_{10}N_2O_2$	208-209	90	Methanol	226.12
2		$C_{13}H_{10}N_2O_3$	185-187	80	Methanol	242.14
3		$C_{14}H_{12}N_2O_2$	164-166	82	Ethanol	240.13
4		$C_{13}H_9N_3O_4$	282-284	60	Pet-ether (40-60)C°	271.11
5		$C_{13}H_9ClN_2O_2$	170-171	81	Pet-ether (40-60) C°	260.52
6		$C_{13}H_9BrN_2O_2$	151-152	85	n-Hexane	305.01
7		$C_{13}H_{10}N_2O_2$	163-166	40	Methanol	226.12



(General Structure)

Table (2) Infrared spectral data of NPA

No.	Name	IR (cm^{-1})
1	N-(3-phthalidyl) 2-amino pyridine	3200(N –H) , 1760 (C=O) , 1590 (C=C)
2	N-(3-phthalidyl)3-hydroxy-2-aminopyridine	3320 (O-H) , 3230 (N-H) , 1715 (C=O) , 1600(C=C)
3	N-(3-phthalidyl) 4-methyl -2-aminopyridine	3300 (N-H) , 1730(C=O) , 1590(C=C)
4	N-(3-phthalidyl)5-nitro- 2-aminopyridine	3250(N-H) , 1740(C=O) , 1600(C=C) , 1580 , 1330 (NO_2)
5	N-(3-phthalidyl) 5-chloro 2-aminopyridine	3180(N-H), 1740(C=O) , 1580(C=C), 880(C-Cl).
6	N-(3-phthalidyl) 5-bromo -2-aminopyridine	3185(N-H), 1740(C=O) , 1570(C=C) , 880(C-Br)
7	N-(3-phthalidyl)-3-aminopyridine	3200(N-H) ,1730 (C=O) , 1570 (C=C).

Table 3: Analytical Data of NPA

NPA No.	Mol.formula	Elemental analysis calculated (found) %		
		C	H	N
1	$C_{13}H_{10}N_2O_2$	69.02 (69.16)	4.46 (4.58)	12.38 (12.36)
2	$C_{13}H_{10}N_2O_3$	64.46 (64.60)	4.16 (4.42)	11.56 (12.68)
3	$C_{14}H_{12}N_2O_2$	69.99 (69.78)	5.03 (5.20)	11.66 (11.68)
4	$C_{13}H_9N_3O_4$	57.67 (57.72)	3.34 (3.43)	15.49 (15.58)
5	$C_{13}H_9N_2O_2Cl$	59.90 (60.02)	3.48 (3.67)	10.75 (10.74)
6	$C_{13}H_9N_2O_2Br$	51.17 (51.22)	2.97 (2.88)	9.18 (9.24)
7	$C_{12}H_{10}N_2O_3$	69.02 (69.29)	4.46 (4.60)	12.38 (12.40)

References

Al Hamdany R., Fataftah,Z., Mahrath A.J., (2003). Toxic.And Inviron.Chem.. 85,4-6,149-157.

Bell, R.P.& Cox, B.G.(1971). J.Chem. Soc.B., 11,2247.

Giovanni S. & Giuseppe, C. (1990).Gazz Chim (Ital) 120, 13 (1990) chemical abstract.113,40113x.

Kenneth B. and Koch.A.M (1983).J.Org.Chem. 48 ,635.

Lin Zhigui,Yongtain, S. and Zhong Caoyao, (1982). 13(2), 17,97,174444.

Ogawa ,Yoshimitu, and Chim, J.P.(1988). 6383, 13, 128818 j,.

Qing Chang, Xiao Ling Wang,(2002).Journal of Pharmacology,1,2.

Tsi D. and Tan B.K.H. (1997).Phototherapy Research, 11, 576 .

Watanbe,Y. (1976).Bull. Chem.Soc.JPh,48(9),2490,84, 120804w.

Wheeler, D.D. & Young, D.C.(1975). J.Org.Chem., 22,547.

Wheeler, DD. And Young D.C.(1961). Pat: U.S. No.9971, 481, (1958). 55,2577.

Xu H.K. and Feng. Y.P.(2000).Acta Pharmacol Sin., 21(5)453.

Zhang J., Peng X, Wei G, Su D. Clin. (1999) Pharmacology 26 (10) 845-6.

Zhongguo Yao Li ,XueBao. (1999) . Medical Sciences ,20 (10),929-33.